DRUG DETERMINATION POLICY

Title: DDP-26 Antilipemic Specialty Agents

Effective Date: 12/13/23

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs that require prior approval.

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and angiopoietin-like protein 3 (ANGPTL3) inhibitors are specialty drugs indicated for specific diseases with hyperlipidemia. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses.

3.0 Clinical Determination Guidelines:

Document the following with chart notes:

I. General Considerations:

A. Appropriate medication use [must meet all listed below]

1. Diagnosis: meets standard diagnostic criteria that designates signs, symptoms, and test results to support specific diagnosis.

2. Food and Drug Administration (FDA) approval status [must meet one listed below]:

a. FDA approved: product, indication, and/or dosage regimen.

b. Non-FDA approved use: Compendium support (Lexicomp®) for use of a drug for a non-FDA approved indication or dosage regimen.

3. Place in therapy: sequence of therapy supported by national or internationally accepted guidelines and/or studies (e.g., oncologic, infectious conditions).

B. Required site-of-care as determined by the Health Plan (DDP-08 Site of Care for Administration of Parenteral Specialty Drugs).

C. Pharmaceutical sample use: The Plan does not recognize samples as a medication trial or for continuation of therapy.

D. Adherence to requested medication required for re-approval [must meet one listed below]:

1. Medications processed on the medical benefit: consistent utilization history documented in claims history or chart notes.

2. Medications processed on the pharmacy benefit: consistent fill history electronically or verbally from a pharmacy.

II. PCSK9 inhibitors: Repatha subcutaneous (evolocumab SQ)

A. Age: at least 10 years old.

B. Diagnosis and severity.

1. Homozygous Familial Hypercholesterolemia (HoFH) [must meet one listed below]:

a. Genetic testing: confirmed presence of two mutant alleles (LDLR, APOB, PCSK9, LDLRAP1 gene).

b. Untreated with low-density lipoprotein (LDL) above 500mg/dL or treated LDL-C above 300mg/dL [must meet one listed below]:

i. Increased LDL-C consistent with HoFH in both parents.

2. Heterozygous Familial Hypercholesterolemia (HeFH) [must meet one listed below]:

a. Dutch Lipid Clinical Network criteria: defined by a total score greater than 8.

b. Simon Broome diagnostic criteria: Adult: total cholesterol above 290mg/dL or LDL-C above 190mg/dL.

3. Atherosclerotic Cardiovascular Disease (ASCVD): Primary or secondary prevention of cardiovascular disease

C. Other therapies [must meet all listed below]:

1. Non-pharmacological: lifestyle modifications attestation from the practitioner.

2. Pharmacological: statin therapy [must meet one listed below]:

a. Contraindication: chronic active liver disease diagnosis for greater than three months and/or unexplained persistent increased serum transaminases.

b. Inadequate response to high-intensity statins and combination therapy for four months [must meet all listed below]:

i. Atorvastatin 40 to 80mg per day and rosuvastatin 20 to 40mg per day.

ii. High-intensity statin with additional lipid-lowering agents such as a fibrate or ezetimibe.

iii. LDL-C within the last month: at least 100mg/dL with ASCVD or at least 130mg/dL without ASCVD.

c. Significant adverse effects lasting two weeks [must meet both listed below]:

i. Muscle symptoms: myalgia, myositis, or rhabdomyolysis.

ii. High-intensity statin dosage reduction or statin re-challenge with low-intensity statin and reappearance of muscle symptoms.

D. Dosage regimen.

1. Repatha subcutaneous (evolocumab SQ):

a. Homozygous familial hypercholesterolemia: 420mg once monthly; may increase to 420mg once every 2 weeks if clinically meaningful response is not achieved in 12 weeks.

i. Patients receiving lipid apheresis may begin at 420mg once every 2 weeks.

b. Heterozygous familial hyperlipidemia: 140mg once every 2 weeks or 420mg once monthly.

c. Hyperlipidemia, primary or secondary prevention of cardiovascular event: 140mg once every 2 weeks or 420mg once monthly. For Adults (18 years +) only

E. Approval.

1. Initial: six months.

2. Re-approval: one year [must meet one listed below]:

a. Absolute reduction LDL-C at least 40mg/dL.

b. LDL-C goal: see Appendix I

F. Exclusions:

1. Excluded drugs: Praluent subcutaneous (alirocumab SQ).

a. Trial of all preferred formulary agents is required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

2. Pregnant or breastfeeding.

3. Women of childbearing potential not using effective contraceptive methods for the duration of PCSK9 inhibitor therapy.

4. Triglycerides above 400mg/dL.

III. ANGPTL3 inhibitor: Evkeeza intravenous (evinacumab-dgnb IV).

A. Age: at least five years.

B. Diagnosis and severity.

1. Homozygous Familial Hypercholesterolemia (HoFH) [must meet one listed below]:

a. Genetic testing: the confirmed presence of two mutant alleles (LDLR, APOB, PCSK9, or LDLRAP1 gene)

b. Untreated with low-density lipoprotein (LDL) above 500mg/dL or treated LDL-C above 300mg/dL [must meet one listed below]:

i. Increased LDL-C consistent with HoFH in both parents.

C. Other therapies [must meet all listed below]:

1. Non-pharmacological: lifestyle modifications (e.g., diet, alcohol use, tobacco cessation, or exercise) attestation from the practitioner.

2. Pharmacological: statin therapy [must meet one listed below]:

a. Contraindication: chronic active liver disease diagnosis for greater than three months and/or unexplained persistent increased serum transaminases.

b. Inadequate response to high-intensity statins and combination therapy for four months [must meet all listed below]:

i. Atorvastatin 40 to 80 mg per day and rosuvastatin 20 to 40 mg per day.

ii. High-intensity statin with additional lipid-lowering agents such as fibrate or ezetimibe.

iii. LDL-C within the last month: at least 100 mg/dL with ASCVD or at least 130 mg/dL without ASCVD.

c. Significant adverse effects lasting two weeks [must meet both listed below]:

i. Muscle symptoms: myalgia, myositis, or rhabdomyolysis.

ii. High-intensity statin dosage reduction or statin re-challenge with low-intensity statin and reappearance of muscle symptoms.

3. Pharmacological PCSK9 inhibitors therapy (Praluent, Repatha): contraindication, inadequate response after four months, or significant adverse effects to one PCSK9 therapy.

D. Dosage regimen: Evkeeza intravenous (evinacumab-dgnb IV) 15 mg per kg every four weeks.

E. Approval.

1. Initial: four months.

2. Re-approval: one year; meets target LDL and cholesterol to the target range. (See Appendix I)

IV. Antilipemic small interfering ribonucleic acid (siRNA) Agent: Leqvio subcutaneous (inclisiran SQ)

A. Age: at least 18 years old

B. Diagnosis and severity [must meet one listed below]:

1. Heterozygous Familial Hypercholesterolemia (HeFH) [must meet one listed below]:

a. Dutch Lipid Clinical Network criteria: defined by a total score greater than 8.

b. Simon Broome diagnostic criteria: Adult: total cholesterol above 290mg/dL or LDL-C above 190mg/dL.

2. Atherosclerotic Cardiovascular Disease (ASCVD): Secondary prevention of cardiovascular disease [must meet one listed below]:

a. History of cardiovascular (CV) event: acute coronary syndromes, myocardial infarction, angina, coronary or other arterial revascularization procedure, stroke, transient ischemic attack, peripheral arterial disease.

b. High-risk ASCVD: clinically significant coronary heart disease (CHD) diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using a treadmill, stress echocardiography, or nuclear imaging).

3. Primary hyperlipidemia with additional risk factors [must meet one listed below]:

a. Diabetes

b. Framingham Risk Score over 20%

C. Other therapies [must meet all listed below]:

1. Non-pharmacological: lifestyle modifications (e.g., diet, alcohol use, tobacco cessation, or exercise) attestation from the practitioner.

2. Pharmacological: statin therapy [must meet one listed below]:

a. Contraindication: chronic active liver disease diagnosis for greater than three months and/or unexplained persistent increased serum transaminases.

b. Inadequate response to high-intensity statins and combination therapy for four months [must meet all listed below]:

i. Atorvastatin 40 to 80 mg per day and rosuvastatin 20 to 40 mg per day.

ii. High-intensity statin with additional lipid-lowering agents such as fibrates or ezetimibe.

iii. LDL-C within the last month: at least 100 mg/dL with ASCVD or at least 130 mg/dL without ASCVD.

c. Significant adverse effects lasting two weeks [must meet both listed below]:

i. Muscle symptoms: myalgia, myositis, or rhabdomyolysis.

ii. High-intensity statin dosage reduction or statin re-challenge with low-intensity statin and reappearance of muscle symptoms.

3. Pharmacological PCSK9 inhibitors therapy (Praluent, Repatha): contraindication, inadequate response after four months, or significant adverse effects to one PCSK9 therapy.

D. Dosage regimen: Leqvio subcutaneous (inclisiran SQ):

1. Loading dose: 284 mg single injection, again at three months.

2. Maintenance dose: 284 mg every six months thereafter.

E. Approval

1. Initial: Nine months (3 doses).

2. Re-approval: one year; meets target LDL and cholesterol to the target range. (See appendix I)

4.0 Coding

COVERED CODES				
HPCPS Code	**Brand Name**	**Generic Name**	**Billing Units (1 unit)**	**Prior Approval**
J1305	Evkeeza	evinacumab-dgnb	5 mg	Y

EXCLUDED CODES			
HPCPS Code	**Brand Name**	**Generic Name**	**Benefit Plan Reference/Reason**
J130	Leqvio	inclisiran	Covered on the pharmacy benefit with prior approval

Brand Name	Generic Name	Process Through Pharmacy Benefit	Process Through Medical Benefit
Evkeeza	evinacumab-dgnb		x
Leqvio	inclisiran	x	
Repatha	evolocumab	x	

5.0 References, Citations & Resources:

1. Lexi comp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Repatha, Praluent, Evkeeza, Leqvio accessed August 2023.
2. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *NEJM* 2015; 372(16):1489-99.
3. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *NEJM* 2015; 372(16)1500-9.
4. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for the management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017; 23:1-87.
5. Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease.
6. New Cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention? Atherosclerosis 2021;319:51-61
7. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139(25):e1082-e1143. doi:10.1161/CIR.0000000000000625[PubMed 3058677]
8. 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006[PubMed 36031461]

6.0 Appendices:

See pages 9-10.

7.0 Revision History:

Original Effective Date: 08/25/2015

Next Review Date: 11/01/2024

Revision Date	Reason for Revision
7/19	Moved to new format; replaced abbreviations
12/19	Off cycle review; removal of specialist-only prescribing requirement; add bottom LDL threshold level for re-approval as per standard of practice
8/20	Annual review, formatting, added other therapies language, replaced abbreviations, simplified text on target lipid levels
6/21	Off cycle review, added section on Evkeeza, modified purpose section
7/21	Off cycle review, changed title, added age and other therapies for PCSK9s, replaced abbreviations
11/21	Off cycle review; exclusion of Repatha for 2022, Added Appendix I with LDL-C goal, removed pediatric info (Praluent has no Ped indication
10/22	Off cycle review, added Leqvio all sections; clarified Praluent dosing per indication; formatting; clarification of 2 mutant alleles for hyperlipidemia tabled at August meeting
8/23	Annual review: Evkeeza expanded indication from 12yo down to 5yo.; added general considerations section, added Leqvio dosage, added Leqvio expanded indication primary hyperlipidemia, added reference; updated coding section, fixed formatting, Praluent excluded, Repatha added

Appendix I: LDL-C Goal [6]

LDL-C goals and thresholds from European and US lipid-lowering guidelines.

CV risk category	ESC/EAS 2019 [1]	AHA/ACC 2018 [2]
Definition		
VHR	Documented ASCVD, includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation, stroke and TIA, and PAD. DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years). Severe CKD (eGFR <30 mL/min/1.73 m^2) SCORE ≥10% for 10-year risk of fatal CVD FH with ASCVD or with another major risk factor.	History of multiple major ASCVD events (recent ACS within the past 12 months, history of MI or ischaemic stroke, symptomatic PAD) or one major ASCVD event and multiple high-risk conditions[a].
High risk	Markedly elevated single risk factors, in particular, total cholesterol >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL) or BP ≥ 180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). SCORE ≥5% and <10% for 10-year risk of fatal CVD.	AHA/ACC cardiovascular risk calculator estimate ≥20% for 10-year risk for ASCVD. Patients with severe hypercholesterolaemia (≥4.9 mmol/L [≥190 mg/dL]). Patients with DM and LDL-C ≥1.8 mmol/L (≥70 mg/dL).
Moderate risk	Young patients (T1DM < 35 years; T2DM < 50 years) with DM duration <10 years, without other risk factors. SCORE ≥1% and <5% for 10-year risk of fatal CVD.	AHA/ACC cardiovascular risk calculator estimate 5% to <7.5% (borderline); 7.5% to <20% (intermediate) for 10-year risk for ASCVD. Patients without DM and LDL-C levels ≥1.8 mmol/L (≥70 mg/dL).
Low risk	SCORE <1% for 10-year risk of fatal CVD.	AHA/ACC cardiovascular risk calculator estimate <5% for 10-year risk for ASCVD.
Treatment threshold for LDL-C reduction		
VHR	Reduce LDL-C levels ≥50% and LDL-C goal of <1.4 mmol/L (<55 mg/dL). Goal LDL-C of <1.0 mmol/L (<40 mg/dL) for patients with ASCVD who experience a second vascular event within 2 years while taking maximally tolerated statin therapy.	LDL-C <1.8 mmol/L (<70 mg/dL).
High risk	Reduce LDL-C levels ≥50% and LDL-C goal ≥1.8 mmol/L (≥70 mg/dL).	LDL-C <2.6 mmol/L (<100 mg/dL). Reduce levels ≥50% in patients with DM and LDL-C ≥1.8 mmol/L (≥70 mg/dL).
Moderate risk	LDL-C <2.6 mmol/L (<100 mg/dL).	Clinician-patient risk discussion before starting statin. Reduce LDL-C levels by ≥ 30% in patients without DM and LDL-C levels ≥1.8 mmol/L (≥70 mg/dL).
Low risk	LDL-C <3.0 mmol/L (<116 mg/dL).	Clinician-patient risk discussion.
Recommended pharmacologic treatment		
VHR	Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe. In patients with ACS and LDL-C levels not at goal despite maximally tolerated statin plus ezetimibe, early initiation of PCSK9 inhibitor should be considered. PCSK9 inhibitor may be considered in patients at VHR not achieving target LDL-C goal on maximally tolerated statin and ezetimibe.	Maximally tolerated statin to lower LDL-C levels by ≥ 50%. Add ezetimibe to maximally tolerated statin when LDL-C level remains ≥1.8 mmol/L (≥70 mg/dL). Add PCSK9 inhibitor to maximally tolerated statin when LDL-C level remains ≥1.8 mmol/L (≥70 mg/dL).
High risk	Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe.	High-intensity statin therapy. Add ezetimibe to high-intensity statin if LDL-C level remains ≥1.8 mmol/L (≥70 mg/dL).
Moderate risk	Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe.	Clinician-patient risk discussion before starting statin. Moderate-intensity statin in patients with DM and LDL-C ≥1.8 mmol/L (≥70 mg/dL); reasonable to add ezetimibe or bile acid sequestrant in patients who would benefit from more aggressive LDL-C lowering. In patients with borderline risk, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin.
Low risk	Maximally tolerated statin to achieve target LDL-C goal; if goal is not reached, add ezetimibe.	Clinician-patient risk discussion.

ACC, American College of Cardiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, Systematic Coronary Risk Estimation; T1DM/T2DM, type 1/2 diabetes mellitus; TIA, transient ischaemic attack; VHR, very high risk.

[a] Multiple high-risk conditions include age ≥65 years, heterozygous FH, history of congestive heart failure, prior coronary artery bypass graft or percutaneous coronary intervention, DM, hypertension, CKD, current smoking, persistently elevated LDL-C ≥2.6 mmol/L (≥100 mg/dL) despite maximally tolerated statin therapy and ezetimibe.

Appendix II: Monitoring & Patient Safety

Drug	Adverse Reaction	Monitoring Parameters	REMS
Praluent alirocumab SQ	• Local: injection site reactions (7-17%) • Pregnancy: adverse events not observed in animal studies;	• Labs: LDL-C within 4-8 weeks of start or dose titration. • Miscellaneous: hypersensitivity to prescription.	Not needed
Evkeeza evinacumab-dgnb IV	• Respiratory: nasopharyngitis (16%)	• Labs: LDL-C when clinically appropriate (2 weeks minimum) • Hypersensitivity • Pregnancy (prior)	Not needed
Leqvio subcutaneous (inclisiran SQ)	• Local: Injection site reaction (4% to 17%, erythema, pruritus, pain, swelling and/or tenderness at injection site)	• Labs: Lipid profile before prior,1-3 months post, then every 3 to 12 months thereafter • Monitor for hypersensitivity reactions.	Not needed